COMMENTS

for

"Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices," Proposed Rule, 63 Fed. Reg. 31143 (June 8, 1998)

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Comments

These comments are submitted by the Massachusetts Biotechnology Council ("MBC") in response to the Proposed Rule on "Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices," Proposed Rule, 63 Fed. Reg. 31143 (June 8, 1998) ("the Proposed Rule). The Proposed Rule sets forth FDA's draft regulations for implementing Section 401 of the FDA Modernization Act of 1997 ("FDAMA"). Section 401 permits the previously prohibited dissemination of medical and scientific information on unapproved uses of marketed drugs, biologics, and devices ("drugs") to health care professionals to ensure such professionals have the best information available when treating patients and making health care decisions. Congress carefully balanced the need for this information with the FDA's desire for accurate research on new uses of approved products when drafting Section 401. The very detailed statutory scheme itself attests to Congress' careful balancing act. The FDA's Proposed Rule, however, would place significant restrictions that extend beyond the well-defined criteria for dissemination articulated in the statute.

I. SUMMARY

MBC has reviewed PhRMA's comments on the Proposed Rule and strongly supports the positions articulated therein. MBC urges the FDA to promulgate a Final Rule which incorporates the recommendations set forth in PhRMA's comments. In addition, the MBC is submitting its own comments in this document to provide more detail on those areas of the Proposed Rule that are of concern to the biotechnology industry. Specifically, MBC finds the Proposed Rule too restrictive in outlining the criteria delineating acceptable journal articles and reference texts; in the level of detail required for the mandatory disclosures and in the manner in

which such statements must be displayed; and in defining "economically prohibitive" and "unapproved uses" so narrowly.

II. BACKGROUND

MBC represents the Massachusetts biotechnology and pharmaceutical industry which consists of a community of approximately 200 mostly small companies. The research and development initiatives of many Members are reaching the clinic and several companies have introduced breakthrough products into national and international health care markets. MBC recognizes that FDAMA is the embodiment of overwhelming bipartisan support for the safe and expeditious commercialization of innovative health care products in general. With Section 401, FDAMA envisioned the dissemination of scientific and medical information on unapproved uses of drugs to health care professionals to provide such professionals with the relevant information necessary to treat patients and make informed health care decisions.

III. COMMENTS

A. THE CRITERIA IN THE PROPOSED RULE DELINIATING ACCEPTABLE JOURNAL ARTICLES AND REFERENCE TEXTS IS TOO RESTRICTIVE.

In the Preamble, as well as the Proposed Rule itself, the FDA sets forth limitations and overly restrictive criteria for defining which journal articles and reference texts are acceptable for dissemination under Section 401. The Proposed Rule circumscribes the number of journal articles eligible for distribution. Section 401 explicitly requires that journal articles be "about a clinical investigation. . . that would be considered scientifically sound by experts." The MBC does not contest the statutory requirement that the article concern a clinical investigation; however, it questions the additional reporting requirements promulgated in the Proposed Rule. As currently drafted, the Proposed Rule requires a journal article to contain a burdensome level of detail beyond that which is generally included in such articles. The additional information does not necessarily improve the quality or scientific value of the article. For example, the regulatory requirement for a "reasonably comprehensive presentation of the study design, conduct, data, analyses and conclusions," coupled with the further evidentiary requirements of the Preamble (including specific reference to: prospective planning, enrollment, population

statistics and follow-through, clinically meaningful endpoints/reasonable surrogate endpoints, well-described treatment regimens, appropriate control groups, adequate adverse experience information, and scientifically appropriate analysis) seems designed to create artificial hurdles for qualification of any particular article for dissemination under Section 401. MBC does not oppose well-designed and well-conducted studies; nor does MBC object to the scientifically sound reporting of those studies. MBC, however, does object to the extensive list of facets which much be reported in the article. Such comprehensive clinical report data is not generally included in peer reviewed articles. The absence of one insignificant element could prohibit the dissemination of a scientifically sound article replete with cutting edge information. For example, even though an article has undergone a rigorous review and acceptance procedure, been published in a highly reputable journal, and authored by a leading expert in the area; its failure to explicitly account for every patient, including the one who discontinued therapy prematurely because his schedule conflicted with the study follow-up schedule, will prevent its dissemination under Section 401. Accordingly, MBC maintains that if an article is published in a peer-reviewed journal and has passed the rigorous review criteria of the journal's scientific and/or editorial panels, the FDA should permit its dissemination under Section 401.

Furthermore, even if the FDA chooses not to adopt the peer-reviewed journal standard noted above as the appropriate interpretation of the "scientifically sound" standard set forth in the statute, the requirement that highly detailed clinical information be included in a publication in order for it to be eligible for dissemination under Section 401 would not be in keeping with the stated rationale of that section. Detailed clinical studies must be submitted to the FDA as part of an SNDA to obtain approval for the new use *within 36 months* of dissemination of any journal article discussing that use. The criteria outlined in the Preamble to the Proposed Rule, however, appears identical to the criteria required to file an SNDA for the new indication. If the manufacturer had sufficient information in hand to file an SNDA, Section 401 would be unnecessary. Congress included Section 401, after extensive debate, to specifically allow for the dissemination of articles that are "scientifically sound" *prior to* the submission of a SNDA. Such

"scientifically sound" studies could be derived from IND or non-IND studies that may not necessarily meet the criteria cited in the Proposed Rule, but would meet strict publication peer-review criteria. MBC urges the FDA to allow the dissemination of such information under Section 401, with the inclusion of appropriate fair balance information, including the known efficacy and safety data for the unapproved use. To encourage the dissemination of information on unapproved uses as foreseen by Congress, MBC suggests the deletion of the specific criteria cited in the Preamble and the Proposed Rule. At a minimum, MBC urges the FDA to adopt the following modifications of the criteria:

1. Any article which has satisfied a journal's peer-review criteria should be presumed to meet the statute's "scientifically sound" criteria;

2. Open label studies should not jeopardize the status of an article otherwise acceptable for dissemination; and

3. Prospective planning of the study according to a protocol should not have to meet IND criteria, as some published information on new uses could be derived from non-IND studies, including, for example, published epidemiological studies.

Since no reference texts reports individual clinical studies in the "reasonably comprehensive manner" proposed by the FDA, the sum total of reference texts permitted to be disseminated under the Proposed Rule constitutes an empty set. This disregards the explicit inclusion of reference texts in the language of Section 401 and the MBC urges the FDA to delete this requirement and accept the dissemination of peer-reviewed reference texts.

B. THE PROPOSED RULE IS TOO RESTRICTIVE BOTH IN THE LEVEL OF DETAIL REQUIRED FOR THE MANDATORY DISCLOSURES AND IN THE MANNER IN WHICH SUCH STATEMENTS MUST BE DISPLAYED.

The Proposed Rule overly extends the statutory provision that disclaimers be "prominently displayed" and is too restrictive both in the level of detail required for disclosures and the manner in which such statements must be displayed. In fact, the Proposed Rule attempts to delineate the precise language of the disclaimer for every article, regardless of the specific content of the article. In addition the rule requires that "any additional information required by the FDA . . . . be attached to the front of the disseminated information. . . " A health care professional reviewing the multitude of attachments, bibliographies, and disclaimers will never reach the information on the unapproved use. The MBC supports the use of clear and effective disclaimers mandated by the statute, including a fair balance statement discussing the known safety and efficacy profile of the new use. The Proposed Rule, however, creates a burdensome amount of paperwork that would discourage rather than encourage the health care professional to review the medical and scientific information disseminated. MBC recommends the FDA permit companies flexibility regarding placement, font, and content of the required disclaimers. In addition, MBC suggests FDA delete the requirement that additional information be attached to the front of the article prior to dissemination.

C. THE PROPOSED RULE RENDERS THE ECONOMICALLY PROHIBITIVE EXEMPTION INEFFECTIVE.

Section 401 provides for a limited exemption to the SNDA filing requirement, where such a filing would be "economically prohibitive." MBC notes that Congress' intent in drafting this exemption was indeed for a limited exemption, however, the Proposed Rule effectively prevents the application of Section 401 in any case where it is not economically feasible to pursue an SNDA. As an alternative to FDA's proposal, MBC suggests the FDA require a manufacturer submit a certified accountant's opinion on the economic feasibility of filing an

SNDA with the material it proposes to disseminate. The FDA may contest the claim of economic prohibition by providing a certified accountant's statement to the contrary.

D. THE DEFINITION OF "UNAPPROVED USES " PROVIDED IN THE PROPOSED RULE IS TOO NARROW.

The definition of "unapproved uses" should not include information derived from clinical studies already reviewed by FDA in a NDA/PLA/BLA filing or supplement, but not included in the approved labeling. The final labeling on an approved drug is the result of extensive negotiation between the agency and the company. Due to space constraints, all clinical information is not included on the final label. Because of this discrepancy, MBC suggests that the FDA should treat such information as promotional and review it according to current procedures for review of promotional material. Such information should not be governed by the more restrictive standards regulating the distribution of "off-label" information pursuant to Section 401.

E. THE FDA SHOULD EASE THE BURDEN OF THE STATUTORY REPORTING REQUIREMENTS BY PERMITTING REPORTING VIA THE INTERNET.

MBC suggests that the FDA permit the required reporting of non-proprietary information (including the original submission to the FDA and the list of articles and reference publications disseminated which must be updated every six months) via the Internet. In addition, the FDA should permit the posting of any balancing articles on the Internet, provided the Internet address is prominently displayed on the article being disseminated. (The FDA currently permits a similar type of Internet information balancing in direct-to-consumer television advertising.) Such a procedure would greatly reduce the paperwork burden, as well as provide a continous source of up-to-date information.

IV. CONCLUSION

In light of the foregoing comments, MBC urges FDA to alter its proposed Rule as outlined above and promulgate a Final Rule that permits a more comprehensive flow of information on unapproved uses to health care professionals. We welcome the opportunity to discuss these comments with you further.